IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:	
RIEPING, Mechthild	Art Unit: 1656
Appl. No.: 10/812,315	Examiner: A. Kim
Filed: March 30, 2004	Atty. Dkt.: 7909/81000
For: **Process for L-Amino Acid Production Using Strains of the Enterobacteriaceae Family**	Conf. No: 1764

Amended Brief on Appeal to the Board of Patent Appeals and Interferences Under 37 C.F.R. 41.37

MS APPEAL BRIEF – PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

A Brief on Appeal was filed in this case on May 9, 2008. On May 20, 2008, a Notification of Noncompliant Appeal Brief was received indicating that the Brief was defective because it failed to properly list the status of the claims in the application.

Separately, on May 29, 2008, twenty days after Appellant filed the original Brief on Appeal, an Interview Summary was mailed indicating that one of the rejections Appellant believed to have been withdrawn, a rejection under 35 U.S.C. § 102(a), was not, in fact, withdrawn.

Therefore, Appellant submits this amended Brief on Appeal to address both communications received from the U.S. Patent and Trademark Office. No fees are believed to be due in connection with this filing, but if that is incorrect and fees are due, the fees may be charged to our Deposit Account No. 50-4056 under our Order No. 7909/81000.

I. Real Party in Interest - 37 C.F.R. § 41.37(c)(1)(i)

The inventor named on the above-captioned application has executed an Assignment transferring all right, title and interest in the application to Degussa AG. On June 24, 2004, the Assignment was recorded at the United States Patent and Trademark Office on Reel 014774, Frame 0948. Thus, the real party in interest in this case is Degussa AG and its successors and assigns.

II. Related Appeals and Interferences - 37 C.F.R. § 41.37(c)(1)(ii)

Appellant is not aware of any other appeals or interferences that will directly affect, be directly affected by, or have a bearing on the Board's decision in the present appeal.

III. Status of the Claims - 37 C.F.R. § 41.37(c)(1)(iii)

Claims 1-12 have been canceled, and the claims now pending in the application are 13-26. Of those claims, claims 13-20 have been allowed. Claims 21-26 are rejected, and are the subject of this appeal. The claims involved in this appeal may be found in the Appendix of this Brief.

IV. Status of the Amendments - 37 C.F.R. § 41.37(c)(1)(iv)

Two of the three amendments submitted by Appellant subsequent to final rejection have been entered into the application. Specifically, the amendment and response filed September 28, 2007 with claim amendments and remarks was entered, the supplemental response filed March 14, 2008 with a verified translation of the priority document into English was entered, but the supplemental response filed March 19, 2008 with claim amendments was not entered.[1]

V. Summary of the Claimed Subject Matter - 37 C.F.R. § 41.37(c)(1)(v)

There is only one independent claim involved in this appeal, claim 23. This is directed to a method for producing an L-amino acid chosen from the group consisting of L-threonine, L-isoleucine, L-valine, L-methionine, L-homoserine and L-lysine by fermenting a bacterium comprising an overexpressed endogenous DNA sequence encoding the galactose-proton symporter protein (the protein has the amino acid sequence of SEQ ID NO:4) in the bacterium. In the claimed method, the bacterium is of the Enterobacteriaceae family and transports glucose by the PEP-dependent phosphotransferase (PTS) pathway. The overexpression of the DNA

[1] Due to a U.S. Patent and Trademark Office error, the supplemental responses filed in March were not considered until May, and Appellant did not receive final notice of the disposition of the March 14, 2008 supplemental

sequence encoding the galactose-proton symporter protein is achieved by increasing the copy number of the DNA or by operably linking the DNA to a promoter. Furthermore, the L-amino acid is produced from glucose, saccharose, lactose, fructose, molasses, starch, cellulose or from glycerine and ethanol, and is allowed to enrich in the culture medium.

General support for this claim may be found, *inter alia*, on page 2, lines 6-19; page 5, lines 18-21; and page 7, lines 25-30, through page 8, line 3. Particular members of the Enterobacteriaceae family that may be used in the method are described on page 8, lines 5-24. A description of the gene encoding the galactose-proton symporter protein and the activity of that protein is found on page 9, line 18 through page 10, line 3. Support for the particular amino acids enumerated in the claim is found on page 18, lines 18-20. Finally, a description of an exemplary procedure that may be used to practice the method is on page 20, lines 1-30.

Claims 24-26, which depends from claim 23, will not be argued separately (i.e., Appellant intends that claims 23-26 stand or fall together).

Claims 21 and 22 are dependent on allowed independent claim 13, and will be argued separately by Appellant. These claims recite a process for producing an L-amino acid using a bacterium that is a member of the Enterobacteriaceae family and overexpresses an endogenous DNA sequence encoding the galactose-proton symporter protein. Claim 21 particularly recites that one or more genes in the bacterium may be overexpressed in addition to the DNA sequence encoding the galactose-proton symporter protein. Support for the claim may be found on page 12, line 16 through page 15, line 22. Claim 22 particularly recites that certain genes in the bacterium may be attenuated. Support for the claim may be found on page 15, line 24 through page 16, line 19.

VI. Grounds of Rejection to be Reviewed on Appeal - 37CFR § 41.37(c)(1)(vi)

Appellant seeks review of (a) the Examiner's rejection of claims 21 and 22 under 35 U.S.C. § 112, second paragraph; (b) the Examiner's rejection of claims 23-26 under 35 U.S.C. § 102(b) in view of Valle, U.S. Patent Application Publication No. 2002/0155521, as evidenced by Blattner, *et al.,* (*Science* 277:1453-1474 (1997)); and (c) the Examiner's rejection of claims 23-26

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response until May 29, 2008, after the original Brief on Appeal was filed, necessitating this Amended Brief.

under 35 U.S.C. § 102(a) in view of Hernandez-Montalvo, *et al.* (*Biotechnol. Bioeng. 83*:687-694 (2003)) as evidenced by Blattner, *et al.* and Lee, *et al.* (*J. Bacteriol. 185*:5442-5451 (1997)).

With respect to the rejection under 35 U.S.C. § 112, in the October 22, 2007 Advisory Action, the Examiner states, "it is unclear if the claims are limited to the one species disclosed in the specification (pages 12-15) or to any gene from other organism [*sic*] which is considered to be an equivalent."

With respect to the rejections under 35 U.S.C. §§ 102(b) and (a), in the October 22, 2007 Advisory Action, the Examiner asserts that in its recitation of "a PEP-dependent phosphotransferase (PTS) pathway," claim 23 reads on the references because that phrase encompasses "any pathway that transport [*sic*] glucose."

VIII. Argument – 37 CFR § 41.37(c)(1)(vii)

A. Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

Claims 21 and 22 have been rejected under 35 U.S.C. 112, second paragraph. In maintaining the rejection in the October 22, 2007 Advisory Action, the Examiner asserts in full that:

> [T]he claims 21 and 22 are not considered to be indefinite. However, as noted previously, it is unclear if the claims are limited to the one species disclosed in the specification or to any gene from other organism [*sic*] which is considered to be equivalent.

Although it is never stated as such, since the claims "are not considered to be indefinite," Appellant believes that the Examiner is asserting that the claims fail to comply with § 112, second paragraph, because they allegedly do not set forth the subject matter that Appellant regards as the invention. Appellant strongly disagrees with the Examiner's position.

The alleged lack of "clarity" arose when, in the March 20, 2007 Amendment, Appellant stated on page 9 of that document that, "it should be clear that the claims do not refer to all forms of the genes but to the specific forms that are presented in the specification. The only other genes encompassed by the claims are those that, under the doctrine of equivalents, would be considered substantially the same as the species defined in the specification."

The Examiner asserts that the last statement in that paragraph, referring to the doctrine of equivalents, is contradictory, and to the best of Appellant's understanding, maintains the rejection on the basis of that allegedly contradictory statement. It is Appellant's position that the claim clearly sets forth the subject matter that Appellant regards as the invention, that no statement offered by Appellant is contradictory, and that there is thus no basis for the rejection.[2]

In the allegedly contradictory statement, Appellant referred to the doctrine of equivalents, a legal doctrine that is applied in construing the claims of issued patents, and has nothing to do with claim construction during prosecution. As the Supreme Court explained in the well-known *Festo* case:

> The language in the patent claims may not capture every nuance of the invention or describe with complete precision the range of its novelty. If patents were always interpreted by their literal terms, their value would be greatly diminished. Unimportant and insubstantial substitutes for certain elements could defeat the patent, and its value to inventors could be destroyed by simple acts of copying. For this reason, the clearest rule of patent interpretation, literalism, may conserve judicial resources but is not necessarily the most efficient rule. The scope of a patent is not limited to its literal terms but instead embraces all equivalents to the claims described.

See *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 622 USPQ2d 1705 (2002).

Thus, the doctrine of equivalents is applied in the interpretation and construction of every issued patent claim for the reasons explained in *Festo*. In making the statement the Examiner incorrectly labels as contradictory, Appellant was merely stating a truism of patent law: if these claims were to be construed in another forum after issuance, that forum would likely construe the claims differently than one would during prosecution and, in particular, would consider the doctrine of equivalents in establishing that claim construction.[3] Therefore,

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[2] "The invention set forth in the claims must be presumed, in the absence of evidence to the contrary, to be that which applicants regard as their invention," see MPEP § 2172, citing *In re Moore*, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971).

[3] In *Solomon v. Kimberly-Clark Corp.*, the Federal Circuit points out the difference between interpreting claims before and after issuance of a patent, stating that, "[a] more limited range of evidence should be considered in evaluating validity as opposed to patentability under either portion of section 112, paragraph 2, because the language of issued claims is generally fixed…the claims are no longer construed as broadly as is reasonably

Appellant respectfully submits that the statement regarding the doctrine of equivalents is not contradictory at all. Instead, it simply reaches beyond the present forum.

Because the statement regarding the doctrine of equivalents is not contradictory, there is no basis for maintaining the rejection under § 112, second paragraph, and the rejection should thus be reversed.

B. Rejection of Claims Under 35 U.S.C. § 102(b)

Claims 23-26 have been rejected under 35 U.S.C. § 102(b) based upon the Valle patent application publication, as evidenced by Blattner, *et al.* The most concise statement of the issue is once again found in the October 22, 2007 Advisory Action, in which the Examiner states:

> Applicants argue "there is only one glucose transport pahtway [*sic*] in the cell that is termed the PEP-dependent phosphotransferase (PTS) pathway," and the PTS pathway is not present in the cells disclosed in the references since the references expressly refer to "PTS-" cells. However, the recitation...in Claim 23 is broader than the disclosure by references. It encompasses any pathway that transport [*sic*] glucose because a glucose or molecule transported (by any pathway into the cell would be phosphorylated) [*sic*] and broken into PEP[.]

Appellant's position on the references has not changed. Specifically, the Valle reference only discloses an increase in gal-P transport in cells without a PTS pathway, i.e., in PTS^- cells, whereas claim 23 recites that the bacterium "transports glucose by the PEP-dependent phosphotransferase (PTS) pathway."

Appellant submits that in maintaining the rejection, the Examiner is giving the phrase "transports glucose by the PEP-dependent phosphotransferase (PTS) pathway" an overly broad construction that is completely at odds with its art-accepted meaning. Contrary to the Examiner's position, the term "PTS pathway" is a specific term of art with a specific meaning – it refers to a particular transport pathway. Evidence of that is found in abundance in the very reference the Examiner cites to make the rejection, Valle, *e.g.,* in FIG. 1, a diagram of glucose transport and processing within a bacterium, where the term "PTS" is prominently used. In the accompanying description, *e.g.*, in paragraph [0005] of Valle, the reference refers to "the PEP-

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possible, and what the patentee subjectively intended his claims to mean is largely irrelevant to the claim's objective meaning and scope," see *Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 55 USPQ2d 1279 (Fed. Cir.

dependent phosphotransferase transport system." Appellant is using the term in claim 23 in the same way that the references are using it.

Therefore, because the term "PTS pathway" has an established, specific meaning in the art and refers to a specific transport pathway, Appellant submits that the Examiner is incorrect in construing it so broadly as to read on any glucose transport pathway.

In maintaining the rejection, the Examiner asserts that certain references of record disclose the existence of other glucose transport pathways. However, that assertion is beside the point – regardless of how many glucose transport pathways there are, there is only one referred to as the "PTS pathway" in the art, and the Valle reference only discloses increases in gal-P transport in bacteria without that pathway. Thus, claims 23-26 are not anticipated, and the rejection should be reversed.

C. Rejection of Claims Under 35 U.S.C. § 102(a)

Claims 23-26 have been rejected under 35 U.S.C. § 102(a) based on the Hernandez-Montalvo, *et al.* reference as evidenced by Blattner, *et al.* and Lee, *et al.*

First, Appellant respectfully submits that the Hernandez-Montalvo, *et al.* reference is not prior art and the rejection should thus be overturned for at least that reason. In the supplemental response filed March 14, 2008, Appellant pointed out that the Hernandez-Montalvo, *et al.* reference has a date after Appellant's priority date and submitted a verified translation of the priority document in order to overcome the reference.

In an Interview Summary form[4] mailed on May 29, 2008, the Examiner states that the verified translation is not sufficient to obviate the rejection under 35 U.S.C. § 102(a) because the "translated Foreign Priority Document does not recite, nor disclose the polypeptide of SEQ ID NO: 4." The Examiner continues that it is "unclear if the recited prior publication in the specification supports the SEQ ID NO: 4."

2000).

[4] The Interview Summary form is not an accurate summary of the conversations between the Examiner and the undersigned. Teleconferences did take place on the date noted, but the content of those conversations was limited to the Examiner's assurance that the verified translation would be entered. There was no specific discussion about support for any particular sequence or feature of any claim. It is Appellant's understanding that the Examiner is using an Interview Summary form instead of sending out another Advisory Action.

It appears that the real issue here is one of differing practices in the U.S. and abroad. To the best of the undersigned's knowledge, German patent applications are not necessarily required to disclose sequence listings as U.S. applications are. Thus, instead of disclosing the explicit sequence listing, the German priority document discloses where and how to find that sequence listing.

More particularly, SEQ ID NO: 4 in the present application is the amino acid sequence of the galactose-proton symporter protein, galP. On page 6 of the verified translation of the priority document, the galP protein is described and several references that disclose it are identified. Additionally, an instruction that "the nucleic acid sequences can be obtained from the databank at the National Center for Biotechnology Information (NCBI) at the National Library of Medicine (Bethesda, MD, USA)" is given with the accession number for that databank, AE000377.

After having compared the galP amino acid sequence under NCBI accession number AE000377 with SEQ ID NO: 4, the undersigned believes and respectfully submits that the two sequences are identical. Thus, Appellant respectfully submits that the galP amino acid sequence, SEQ ID NO: 4 in the present application, is fully supported by the priority document. Therefore, the rejection should be overturned, as the rejected claims are clearly supported by the priority document and are thus entitled to its filing date.

Although Appellant strongly believes that the Hernandez-Montalvo, *et al.* reference is not prior art and the rejection should be overturned for at least that reason, the rejection also fails on its merits. Specifically, this rejection under § 102(a) raises essentially the same issue as the rejection under § 102(b) that is argued above – the Examiner is rejecting the claims because of an improperly broad construction of the term "PTS pathway." Thus, Appellant believes that the arguments made above with respect to the rejection under § 102(b) are equally applicable here.

Additionally, as Appellant pointed out in previous responses to the rejection, the Hernandez-Montalvo, *et al.* reference itself provides additional evidence that there is only one PTS pathway, and that pathway does not include the galactose-proton symporter protein in at least the figure on page 688 of the reference.

Accordingly, for all of the reasons given above, the rejection of claims 23-26 should be overturned.

Conclusion

For the reasons discussed above, Appellant believes that the Examiner is mistaken in his rejection of claims under 35 U.S.C. § 112 and 35 U.S.C. § 102. It is therefore respectfully requested that the Honorable Board reverse the Examiner and remand this application for issue.

Respectfully submitted,

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VIII. Claim Appendix - 37 C.F.R. § 41.37(c)(1)(viii)

13. A process for the production of an L-amino acid chosen from the group consisting of L-threonine, L-isoleucine, L-valine, L-methionine, L-homoserine and L-lysine comprising:

a) fermenting a bacterium comprising an overexpressed endogenous DNA sequence encoding the galactose-proton symporter protein in said bacterium, in a fermentation medium under conditions suitable for the production of said L-amino acid, wherein:

i) said bacterium is of an Enterobacteriaceae family;

ii) said galactose-proton symporter protein comprises the amino acid sequence of SEQ ID NO:4 and is encoded by the nucleotide sequence of SEQ ID NO:3;

iii) said L-amino acid is produced from glucose, saccharose, lactose, fructose, molasses, starch, cellulose or from glycerine and ethanol;

iv) said overexpression is achieved by increasing the copy number of said DNA or by operably linking said DNA to a promoter; and

b) allowing said L-amino acid to become enriched in said bacteria or said fermentation medium.

21. The process of claim 13, wherein said microorganism overexpresses one or more genes selected from the group consisting of:

a) the thrABC operon coding for aspartate kinase, homoserine dehydrogenase, homoserine kinase and threonine synthase;

b) the pyc gene coding for pyruvate carboxylase;

c) the pps gene coding for phosphoenolpyruvate synthase;

d) the ppc gene coding for phosphoenolpyruvate carboxylase;

e) the pntA and pntB genes coding for transhydrogenase,

f) the rhtB gene which imparts homoserine resistance;

g) the mqo gene coding for malate:quinone oxidoreductase;

h) the rhtC gene which imparts threonine resistance;

i) the thrE gene coding for threonine export protein;

j) the gdhA gene coding for glutamate dehydrogenase;

k) the glk gene coding for glucokinase;

l) the hns gene coding for DNA binding protein HLP-II;

m) the pgm gene coding for phosphoglucomutase;

n) the fba gene coding for fructose biphosphate aldolase;

o) the ptsH gene coding for phosphohistidine protein hexose phosphotransferase;

p) the ptsI gene coding for enzyme I in the phosphotransferase system;

q) the crr gene coding for the glucose-specific IIA component;

r) the ptsG gene coding for the glucose-specific IIBC component;

s) the lrp gene coding for a regulator in the leucine regulon;

t) the csrA gene coding for the global regulator Csr;

u) the fadR gene coding for a regulator in the fad regulon;

v) the iclR gene coding for a regulator in central intermediary metabolism;

w) the mopB gene coding for the 10 KDa chaperone;

x) the ahpC gene coding for the small sub-unit of alkyl hydroperoxide reductase;

y) the ahpF gene coding for the large sub-unit of alkyl hydroperoxide reductase;

z) the cysK gene coding for cysteine synthase A;

aa) the cysB gene coding for the regulator in the cys regulon;

bb) the cysJ gene coding for the flavoprotein in NADPH sulfite reductase;

cc) the cysI gene coding for haemoprotein in NADPH sulfite reductase;

dd) the cysH gene coding for adenylylsulfate reductase;

ee) the phoB gene coding for the positive regulator PhoB in the pho regulon;

ff) the phoR gene coding for the sensor protein in the pho regulon;

gg) the phoE gene coding for protein E in the outer cell membrane;

hh) the pykF gene coding for the pyruvate kinase I stimulated by fructose;

ii) the pfkB gene coding for 6-phosphofructokinase II;

jj) the malE gene coding for periplasmatic binding protein in maltose transport;

kk) the sodA gene coding for superoxidedismutase;

ll) the rseA gene coding for a membrane protein with anti-sigmaE activity;

mm) the rseC gene coding for a global regulator in the sigmaE factor;

nn) the sucA gene coding for the decarboxylase sub-unit of 2-ketoglutarate dehydrogenase;

00) the sucB gene coding for the dihydrolipoyl-transsuccinase E2 subunit of 2-ketoglutarate dehydrogenase;

pp) the sucC gene coding for the β-subunit of succinyl-CoA synthetase;

qq) the sucD gene coding for the α-subunit in succinyl-CoA synthetase;

rr) the adk gene coding for adenylate kinase;

ss) the hdeA gene coding for a periplasmatic protein with a chaperonin-like function;

tt) the hdeB gene coding for a periplasmatic protein with a chaperonin-like function;

uu) the icd gene coding for isocitrate dehydrogenase;

vv) the mglB gene coding for periplasmatic, galactose-binding transport protein;

ww) the lpd gene coding for dihydrolipoamide dehydrogenase;

xx) the aceE gene coding for the E1 component of pyruvate dehydrogenase complex;

yy) the aceF gene coding for the E2 component of pyruvate dehydrogenase complex;

zz) the pepB gene coding for aminopeptidase B;

aaa) the aldH gene coding for aldehyde dehydrogenase;

bbb) the bfr gene coding for the iron storage homoprotein;

ccc) the udp gene coding for uridine phosphorylase; and

ddd) the rseB gene coding for the regulator of sigmaE factor activity.

22. The process of claim 13, wherein at least one gene in said microorganism is attenuated, said gene being selected from the group consisting of:

a) the tdh gene coding for threonine dehydrogenase;

b) the mdh gene coding for malate dehydrogenase;

c) the gene product of the open reading frame (ORF) yjfA;

d) the gene product of the open reading frame (ORF) ytfP;

e) the pckA gene coding for the enzyme phosphoenol-pyruvate carboxykinase;

f) the poxB gene coding for pyruvate oxidase;

g) the aceA gene coding for isocitrate lyase;

h) the dgsA gene coding for the DgsA regulator in the phosphotransferase system;

i) the fruR gene coding for fructose repressor;

j) the rpoS gene coding for the sigma^{38}-Factor;

k) the aspA gene coding for aspartate ammonium lyase; and

l) the aceB gene coding for malate synthase A gene.

23. A process for the production of an L-amino acid chosen from the group consisting of L-threonine, L-isoleucine, L-valine, L-methionine, L-homoserine and L-lysine comprising:

a) fermenting a bacterium comprising an overexpressed endogenous DNA sequence encoding the galactose-proton symporter protein in said bacterium, in a fermentation medium under conditions suitable for the production of said L-amino acid, wherein:

i) said bacterium is of an Enterobacteriaceae family and transports glucose by a PEP-dependent phosphotransferase (PTS) pathway;

ii) said galactose-proton symporter protein comprises the amino acid sequence of SEQ ID NO:4;

iii) said L-amino acid is produced from glucose, saccharose, lactose, fructose, molasses, starch, cellulose or from glycerine and ethanol;

iv) said overexpression is achieved by increasing the copy number of said DNA or by operably linking said DNA to a promoter; and

b) allowing said L-amino acid to become enriched in said bacteria or said fermentation medium.

24. The process of claim 23, further comprising isolating said L-amino acid along with some or all of the constituents of said fermentation medium and/or the biomass in said fermentation medium.

25. The process of claim 24, wherein said bacterium is selected from the group consisting of: Escherichia coli H4581; Escherichia coli VNIIgenetika MG442; Escherichia coli VNIIgenetika M1; Escherichia coli VNIIgenetika 472T23; Escherichia coli BKIIM B-3996; Escherichia coli kat 13; and Escherichia coli KCCM-10132.

26. The process of claim 25, wherein said L-amino acid is L-threonine.

IX. Evidence Appendix - 37 C.F.R. § 41.37(c)(1)(ix)

There is no evidence under 37 CFR §§1.130; 1.131 or 1.132 or other evidence entered by the Examiner that Appellant is relying upon on Appeal.

X. Related Proceedings Appendix - 37 C.F.R. § 41.37(c)(1)(x)

Appellant is not aware of any related proceedings for this application.